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CRITICAL REVIEW AND INVITED COMMENTARY

The combination of EEG Source Imaging and EEG-correlated functional MRI to map epileptic networks

***†‡Serge Vulliemoz, *†Louis Lemieux, §¶Jean Daunizeau, ‡Christoph M. Michel and *†John S. Duncan**

***Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, University College London, Queen Square, London, United Kingdom; †MRI Unit, National Society for Epilepsy, Chalfont Epilepsy Centre, Chalfont St Peter, Buckinghamshire, United Kingdom; ‡Epilepsy Unit and Functional Brain Mapping Laboratory, Neurology Department, University Hospital and University of Geneva, Switzerland; §Wellcome Trust Centre for Neuroimaging, UCL Institute of Neurology, Queen Square, London, United Kingdom; and ¶Center for the Study of Social and Neural Systems, Institute of Empirical Research in Economics, University of Zurich, Zurich, Switzerland**

Summary

Functional electrophysiologic techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) give insights into the dynamics of the networks involved in the generation of interictal and ictal epileptic activity and their interaction with physiologic brain activity. With recent advances in methodology and clinical validation, EEG source imaging (ESI) may now be used to map epileptic activity as well as evoked responses to external stimuli. By its ability to show hemodynamic changes time locked to epileptic activity in the whole brain, EEG-correlated functional magnetic resonance imaging (fMRI) (EEG-fMRI) is the natural counterpart of ESI, circumventing some of its limitations, the former adding data from the depths of the brain, and the latter temporal resolution. To better understand the potential and limitations of both techniques, this review starts with a description of the neurophysiologic mechanisms that give rise to the measured signals, followed by validation studies based on comparison with intracranial EEG and surgical outcome. We then discuss analysis strategies to combine both techniques by reviewing studies in epilepsy, current methodologic development, and future directions of this fast-developing field.

KEY WORDS: Epilepsy, fMRI, EEG source imaging.

After the first report of electroencephalography (EEG) recording of the human brain performed by Hans Berger in 1929, study of the brain of epileptic patients quickly followed, notably by William Grey Walter, who applied a larger number of smaller electrodes to localize physiologic and pathologic patterns of electric activity (Niedermeyer & Lopes da Silva, 2005). Clinically, analysis of EEG monopolar or bipolar EEG traces remains the mainstay of EEG interpretation to localize abnormal electrical activity. EEG source imaging (ESI) has transformed conventional EEG analysis into a three-dimensional imaging tool for the localization of epileptic sources (Michel et al., 2004a; Plummer et al., 2008) and evoked potentials (Michel et al., 2001) by estimating the distribution of three-dimensional intracerebral electrical activity giving rise to the recorded scalp activity (He & Lian, 2002; Michel et al., 2004b). ESI allows the investigation of dynamic changes in neuronal networks with a time resolution of milliseconds.

Since the late 1990s, EEG-correlated functional magnetic resonance imaging (EEG-fMRI) has emerged as a noninvasive brain imaging technique based on EEG recording (Hamandi et al., 2004; Gotman et al., 2006; Laufs & Duncan, 2007). Following the first studies on data quality and patient safety (Ives et al., 1993; Lemieux et al., 1997; Allen et al., 1998; Seeck et al., 1998; Krakow et al., 1999; Allen et al., 2000), a growing body of methodologic and clinical studies have transformed EEG-fMRI into a powerful tool to investigate the hemodynamic changes associated with spontaneous brain activity in epileptic networks, including subcortical changes, but also to study endogenous brain rhythms of wakefulness and sleep, as well as evoked brain activity [for reviews, see (Gotman et al., 2006; Ritter & Villringer, 2006; Laufs et al., 2008)].

An expectation of new imaging tools in epileptology is their potential to improve the management of candidates for surgical treatment of their epilepsy. Formal validation of

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Address correspondence to Dr Serge Vulliemoz, MRI Unit, National Society for Epilepsy, Chesham Lane, Chalfont St Peter, Buckinghamshire SL9 0RJ, U.K. E-mail: s.vulliemoz@ion.ucl.ac.uk
Literature search strategy:
We searched PubMed from 1990 to March 2009 for articles containing the key words: Epilep* AND (fMRI EEG source) as well as Epilep* AND (fMRI electr* source). We considered original articles, published in English and French.

localization techniques is difficult, requiring comparison with a gold standard, ideally in large homogenous patient groups. Radiologically visible lesions, which can be relatively large, do often not colocalize with the irritative or ictal onset zones. Validation with intracranial EEG is intrinsically constrained to small groups of patients with heterogeneous epileptic syndromes and limited intracranial spatial sampling. Postoperative seizure freedom in patients in whom the estimated epileptic focus was localized in the resection zone represents the most clinically relevant form of validation. However, the areas resected are often much larger than the epileptic zone, making it difficult to assess the test's specificity, and long-term follow-up is required.

In the following we give an overview of the neurophysiologic background, principles, limitations, and main clinical validation studies of ESI and EEG-fMRI. We then discuss various strategies to combine ESI and EEG-fMRI to study the spatial and temporal organization of epileptic networks and their interaction with background cerebral activity.

Neurophysiologic Background

Origin of the EEG signal

Scalp EEG electrodes record fluctuations in electrical potential caused by the summed excitatory and inhibitory postsynaptic potentials generated by populations of cortical pyramidal neurons, with effective orientation perpendicular to the cortical surface (Niedermeyer & Lopes da Silva, 2005). The solid angle theory applied to EEG generators explains why short-lasting axonal action potentials of about 1-ms duration do not result in a combined macroscopic electric signal, despite frequent firing and high amplitude (Gloor, 1985). Synchronous cortical activity over at least 6–10 cm^2 of gyral surface is necessary for pathologic events to be clearly detectable with scalp electrodes (Tao et al., 2005). The infolding and multilaminar structure of the cortex can make the relationship between generators and electrodes complex (Megevand et al., 2008), and some neuronal activity gives rise to a ''closed'' electric field (e.g., stellate cells), invisible to scalp electrodes (Nunez & Silberstein, 2000).

Origin of the fMRI signal

fMRI studies measure local changes in brain oxygenation by detecting differences in magnetic susceptibility between oxy- and deoxyhemoglobin (blood oxygen level dependent, BOLD, signal changes). The interpretation of fMRI maps relies on the assumption that an increase of regional ''neuronal activity'' results in an increase in metabolic demand, an excessive increase in perfusion, and a decreased concentration of deoxygenated hemoglobin in local venous blood (increase of BOLD signal) (Fig. 1A, B) [See (Buzsaki et al., 2007; Logothetis, 2008) for a detailed neurophysiologic review].

Experimental work in monkeys showed that BOLD increases correlate better with increases in local field potential (representing perisynaptic activity around and extracellular intracranial electrodes over a range of a few millimeters) than with multiunit activity, and constitutes, therefore, a model of synaptic activity. In contrast, the firing of action potentials by neurons is probably too short to trigger a measurable metabolic–vascular response (Logothetis et al., 2001). However, the local field potential (LFP) is only an imperfect measure of synaptic activity, as its fluctuations are not specific to selective changes in network activity. Moreover, postsynaptic activity also contributes to the LFP which preferably reflects synaptic activity of pyramidal cells because of their spatial alignment (Logothetis, 2008).

Changes in neuronal activity and the BOLD signal, described by the hemodynamic response function (HRF) (Glover, 1999), occur over different time scales (Fig. 1C). Spatially, fMRI studies typically use voxels with a volume of the order of 50 mm^3, and are well suited to the anatomic scale of the hemodynamic changes (Logothetis, 2008).

The interpretation of sustained negative BOLD responses observed in animal studies (Shmuel et al., 2006; Maier et al., 2008) as well as neurophysiologic (Shmuel et al., 2002) and epilepsy studies in humans (Kobayashi et al., 2006a; Salek-Haddadi et al., 2006) is difficult and probably context dependent (Fig. 1B). A decrease in metabolism may be associated with a selective increase in neuronal activity (or synchrony), as in the case of the alpha rhythm (Laufs et al., 2006b) or generalized spike and wave discharges (Aghakhani et al., 2004; Hamandi et al., 2006). In localization-related epilepsies, it is not clear whether the observed transient negative BOLD changes reflect surround inhibition, impaired neurovascular coupling, distant downstream/upstream metabolic decrease, propagated epileptic activity or, less probably, a vascular theft mechanism (Kobayashi et al., 2006a; Salek-Haddadi et al., 2006).

EEG Source Imaging (ESI)

Methodologic principles and limitations

ESI can estimate the localization of the electric source(s) within the brain volume, which generate interictal epileptiform discharge (IED) recording with scalp electrodes. The relationship between a specific distribution of postulated electric sources in the brain and the resulting scalp voltage map is determined by the forward model: the construction of a mathematical model of the head's electromagnetic and geometric properties to calculate the volume conduction. These head models can be categorized as either spherical or realistic models; the latter give a more accurate description of individual head and brain morphology but are more computationally demanding. For a given scalp voltage field, there is an infinite number of possible source configurations, giving rise to the famous and fundamental non-unicity of the inverse electromagnetic problem (Helmholtz, 1853). As a

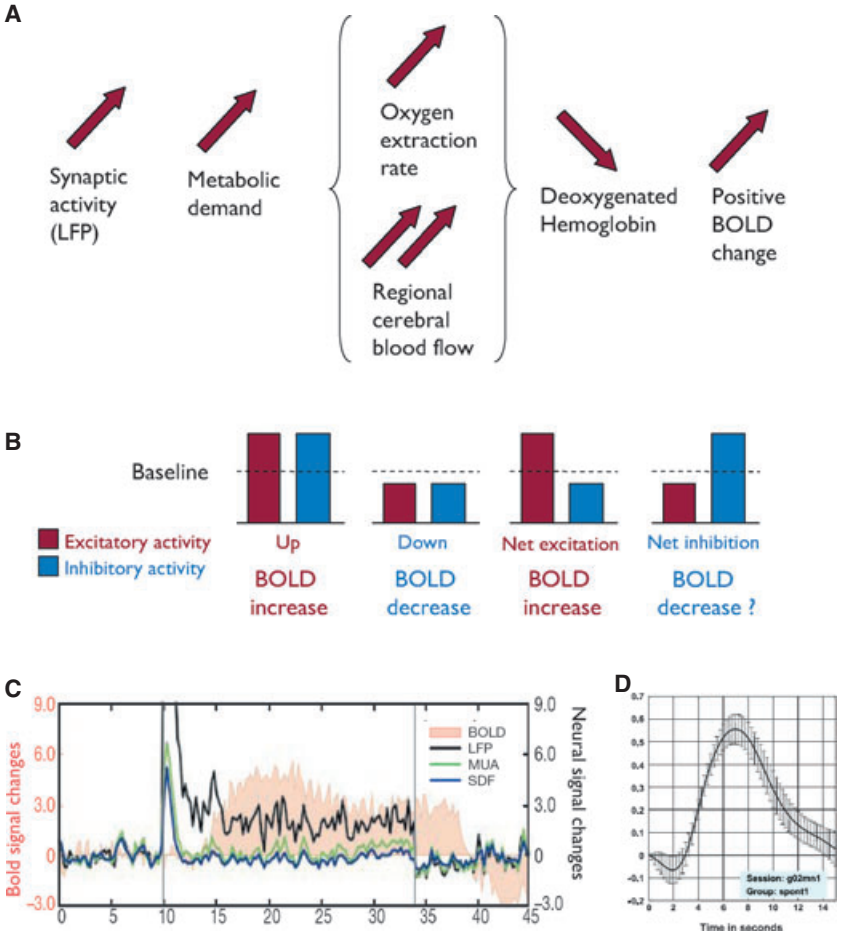

Figure 1.
Neurophysiology underlying the neurovascular coupling and the generation of the blood oxygen level dependent (BOLD) signal recorded with functional magnetic resonance imaging (fMRI). (**A**) A basic assumption underlying the interpretation of fMRI maps is that an increase of regional "neuronal activity" (global synaptic product of a local neuronal population in response to inhibitory and excitatory inputs and interneural feed-forward and feedback activity) results in an increase in metabolic demand (of neurons and astrocytes), with increased energy and oxygen consumption. In response to these neurometabolic changes, there is a rise in local brain perfusion that exceeds the metabolic needs. Therefore, although the total oxygen consumption increases, the fraction of oxygen extraction decreases and the percentage of deoxygenated hemoglobin in local venous blood decreases (positive BOLD change as recorded with fMRI). (**B**) In a neuronal network comprising forward and backward excitatory and inhibitory connections, the BOLD signal changes reflect changes of the network "state" compared to a carefully defined baseline (Logothetis, 2008). Adapted by permission from Macmillan Publishers Ltd: Nature, Logothetis, N. K., What we can do and what we cannot do with fMRI, 453, 869–78, copyright 2008. (**C**) Correlation between the neuronal signals (recorded with intracerebral electrodes) and the hemodynamic response in response to a sustained visual stimulus in monkeys. Changes in local field potential provide the best estimate of the hemodynamic response. Note the lag of the hemodynamic response and slow increase over a time range of several seconds (pink surface curve). LFP, local field potential, MUA, multiunit activity, SDF, spike density function. Adapted by permission from Macmillan Publishers Ltd: Nature, Logothetis, N. K., Pauls, J., Augath, M., Trinath, T. and Oeltermann, A., Neurophysiological investigation of the basis of the fMRI signal, 412, 150–7, copyright 2001. (**D**) Fitted hemodynamic response function (HRF) in response to a stimulus at time = 0 s. Note the initial negative dip followed by a positive maximum after 6–8 s and a slow return to baseline. Reprinted from Magnetic Resonance Imaging, 22, Logothetis, N. K., Pfeuffer, J., On the nature of the BOLD fMRI contrast mechanism, pp 1517–31, Copyright 2004, with permission from Elsevier.

consequence, solving the inverse problem requires assumptions to be made about the sources and the volume conductor, in order to reduce the solution space (number and spatial configuration of possible solutions). Common assumptions for neural sources are equivalent dipoles and so-called distributed solutions. The methodology, applications, and validation of ESI techniques have been addressed in recent comprehensive reviews (Michel et al., 2004b;

Leijten & Huiskamp, 2008; Plummer et al., 2008). Briefly, dipolar solutions estimate the localization and orientation of one or a few equivalent dipole(s) generating a given scalp voltage map as recorded by EEG electrodes. Distributed linear solutions estimate the activity of each point (source) in a solution space (usually the gray matter) and are better suited for extended sources but require further assumption to solve the inverse problem. Dipolar and distributed linear solutions applied to IED localization have been compared, using simulated EEG data (Grova et al., 2006) or clinical recordings (Ebersole, 1999). The result of the comparison depends on the nature of the dataset and the spatial extent of neuronal generators.

High electrode densities (≥64 channels) and extensive spatial coverage, including inferior temporal electrodes, increase the precision of ESI (Kobayashi et al., 2003; Lantz et al., 2003a; Meckes-Ferber et al., 2004; Sperli et al., 2006). Fast neurophysiologic propagation affects the localization and morphology of scalp IED (Alarcon et al., 1994; Fernandez Torre et al., 1999) and ESI is more accurate when applied to the IED rising phase rather than to its peak (Lantz et al., 2003b). The ability of EEG and ESI to visualize medial temporal IED or only their basal or lateral propagation is controversial (Lantz et al., 1997; Pacia & Ebersole, 1997; Merlet & Gotman, 2001; Gavaret et al., 2004; Zumsteg et al., 2006).

Nonparametric or parametric statistical mapping has been used to determine source extent thresholds, similar to the methods applied in MRI and quantitative isotope studies [positron emission tomography (PET), single photon emission computed tomography (SPECT)], with postsurgical (Sperli et al., 2006) or invasive electrophysiologic (Zumsteg et al., 2006) validation. These methods reduce the risk of detecting spurious source and increase sensitivity to weaker source activity (Michel et al., 2004a,b), thereby strengthening the position of ESI as a modern brain mapping technique.

Clinical ESI studies in focal epilepsy

Interictal ESI as a presurgical tool in epilepsy and validation with intracranial EEG and surgical series

Comparison of ESI with invasive EEG recordings has been carried out with simultaneous scalp ESI and *foramen ovale* recordings in patients with temporal lobe epilepsy. ESI was able to differentiate between medial and lateral temporal spikes (Dinesh Nayak et al., 2004; Zumsteg et al., 2006) and to identify patterns of propagation within the temporal lobe. Concordance between intracranial EEG and dipolar sources has been found in >90% of technically feasible cases in temporal and frontal lobe epilepsy (Gavaret et al., 2004, 2006). In another study of patients with both temporal and extratemporal epilepsies recorded with dense-array EEG (128 electrodes), a distributed linear ESI model was concordant at a lobar level in 94% of 32 patients, including 100% of patients with temporal lobe epilepsy (Michel et al., 2004a). Good concordance between ESI and the resection area was obtained in 79% of postoperative seizure-free cases. Finally, ESI can be accurate despite large brain lesions (Brodbeck et al., 2009). Unfortunately, these studies were unblinded and retrospective, and the additional localization information compared to other imaging modalities was not analyzed.

Currently, ESI is not used widely in epilepsy surgery centers. One reason might be that until now, no standard ''good-practice'' has been widely established with respect to the choice of head models and inverse algorithms. Figure 2 shows an example of ESI based on multichannel EEG and a realistic head model in a patient with focal epilepsy and a large brain lesion.

Ictal ESI studies

ESI can also be applied to analyze ictal EEG data (provided adequate number and position of electrodes are used), with the key advantage that ictal events can be more easily recorded as part of routine telemetry investigations than any other modality. Despite methodologic difficulties due to the potentially nonstationary EEG patterns, motion artifacts, and the difficulty in recording multiple identical events, ESI applied to ictal EEG showed good localization when analysis was performed in the time-domain (Lantz et al., 2001; Holmes et al., 2008) or using dominant frequency at ictal onset (Blanke et al., 2000). A few studies have provided validation with intracranial EEG recordings (Assaf & Ebersole, 1999; Merlet & Gotman, 2001; Boon et al., 2002).

EEG-fMRI

Methodologic principles and limitations

Data acquisition and processing:

Technical details regarding EEG-fMRI data acquisition, safety issues, and data analysis have been reviewed recently (Hamandi et al., 2004; Gotman et al., 2006; Laufs et al., 2008). In summary, 19–92 electrodes are commonly used to record the EEG inside the MRI scanner bore. Although some centers still rely on the original technique of spike-triggered fMRI acquisition, fMRI volumes are currently usually acquired continuously, with subsequent correction of the EEG MR-gradient and pulse artifacts. The choice of the optimal approach for EEG correction depends on whether the EEG patterns of interest are of high or low frequency and spontaneous or evoked (Grouiller et al., 2007; Ritter et al., 2007). For fMRI data analysis, IED marked on the corrected EEG recordings are entered into a general linear model (after convolution with a model of the HRF). Center-specific choices of confounds including motion regressors, and cardiac confounds to model other sources of variance of the BOLD signal. The statistical estimation of this model identifies the voxels in which the BOLD signal

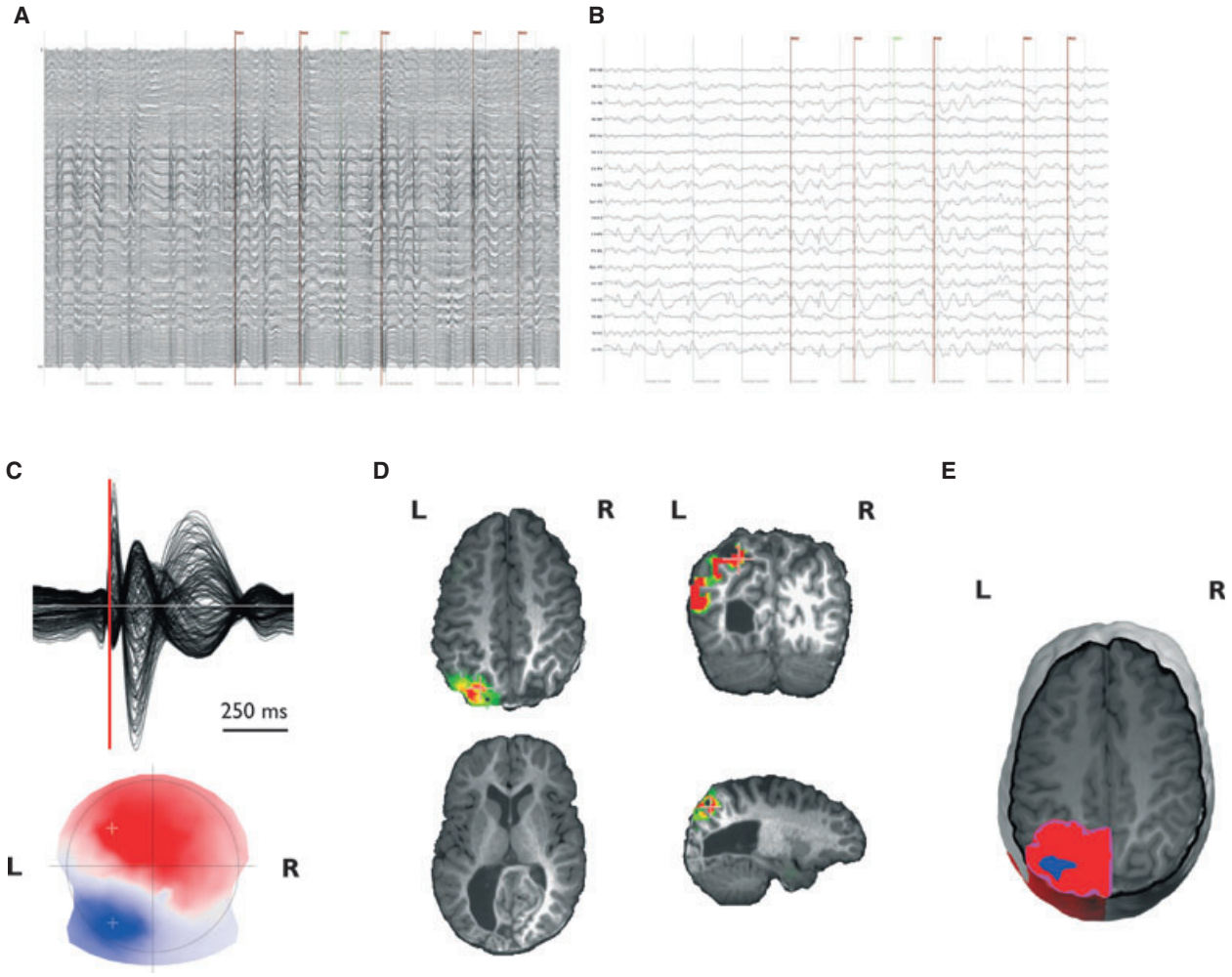

Figure 2.
Electroencephalography (EEG) source imaging (ESI) with dense-array EEG recording, distributed linear solution, and individual head model: 9 year-old girl with daily seizures symptomatic of a large left posterior lesion with frequent parietooccipital interictal epileptiform discharges (IEDs). (**A**) EEG trace obtained with 256 electrodes. (**B**) Same recording viewed with a standard "double banana" bipolar montage for easier identification and categorization of IED. (**C**) Top : average of selected IEDs (all channels superimposed), bottom : map of scalp voltage topography during the first rising phase of the IED (red vertical line in top image), which is the most reliable time frame for localizing IED onset (Lantz et al., 2003b). (**D**) ESI was performed using a distributed linear model (Local AUtoRegressive Algorithm, LAURA) and a spherical head model with individual anatomic constraints to account for the presence of the large left posterior lesion. Results are coregistered to the patient's T_1-weighted magnetic resonance imaging (MRI) and show left parietooccipital activity (red cross line indicates solution point with maximal activity). (**E**) Coregistration of ESI result and resection area on T_1-weighted MRI showing the inclusion of the ESI maximum in the resection zone. The patient is seizure-free after 1 year follow-up. (Courtesy of Dr Brodbeck, Functional Brain Mapping Laboratory, Neurology Department, University Hospital and University of Geneva, Switzerland. For details, see (Brodbeck et al., 2009))

time course is significantly correlated with the occurrence of the IED.

Methodologic considerations

Image distortion and signal dropout are caused notably by air–tissue interfaces (basal temporal lobe, orbitofrontal regions), metal foreign body, hemosiderin deposits (cavernomas, trauma, or surgical sites), and influence the probability of obtaining a response in patients with temporal lobe epilepsy (Bagshaw et al., 2004). Higher field strengths decrease the contribution of potentially confounding draining veins to the signal but increase pulse artifacts and susceptibility artifacts (Mullinger et al., 2008). Independent component analysis (ICA) has been applied to the EEG to select an "epileptic regressor" for fMRI analysis with improved sensitivity compared to IED based approaches,

although formal validation was generally not available (Jann et al., 2008; Marques et al., 2009). ICA has also been used in ''data-driven'' analysis of the fMRI signal to reveal interictal hemodynamic signatures without reference to the EEG (Rodionov et al., 2007).

Intracranial electrodes can record abundant epileptic activity that is not detected with scalp electrodes (Alarcon et al., 1994; Nunez & Silberstein, 2000; Tao et al., 2005), so that precise modeling of the BOLD baseline is difficult. Integration of physiologic background rhythms (Tyvaert et al., 2008b) or the use of ICA of the BOLD signal (Mantini et al., 2007; Rodionov et al., 2007) could improve the sensitivity of EEG-fMRI studies. Simultaneous scalp and intracranial EEG could help to explain why some patients with frequent IED do not show any significant correlated BOLD changes. Ongoing studies are currently evaluating the interactions between intracranial electrodes and MRI (Carmichael et al., 2007, 2008b, 2009), with the aim to improve modeling BOLD signal changes using simultaneous intracranial EEG recordings.

Clinical EEG-fMRI studies in focal epilepsy

Interictal studies

So far, most EEG-fMRI studies in focal epilepsy are exploratory whole-brain studies aimed at demonstrating BOLD changes throughout the brain linked to any pathologic discharges on scalp EEG. The yield of BOLD responses is predominantly affected by EEG criteria (IED frequency). EEG-fMRI studies on patients with malformations of cortical development found changes extending beyond the radiologic structural abnormalities consistent with histologic and intracranial electrophysiologic studies (Salek-Haddadi et al., 2002; Kobayashi et al., 2005, 2006b; Salek-Haddadi et al., 2006).

Validation of EEG-fMRI in epilepsy: intracranial EEG and surgical series

Comparison of EEG-fMRI results with other localizing tools has shown promising results regarding the clinical relevance of EEG-fMRI findings. EEG-fMRI results were concordant with interictal hypometabolism on PET and ictal hyperperfusion using SPECT in seven adults with various epileptic syndromes (Lazeyras et al., 2000). When available, intracranial recordings confirmed the findings in five of six patients. Concordance with PET (two patients) and SPECT (two patients) was also reported in a pediatric study (De Tiege et al., 2007). Benar et al., (2006) found good agreement between clusters of BOLD response and intracranial spiking contacts in five patients but did not analyze the correlation between the most significant BOLD cluster and the most active interictal contact or the ictal onset zone. In another study on an overlapping group of patients, congruence between interictal intracranial EEG and EEG-fMRI results was found in three of eight patients in whom intracranial EEG was available (Grova et al., 2008). More interestingly, propagation of IED recorded by intracranial electrodes has been shown to occur from the vicinity of one BOLD cluster to another (Grova et al., 2008; Vulliemoz et al., 2009b). BOLD response to focal slow EEG activity instead of IED was shown to be concordant with the ictal onset zone on intracranial EEG findings in one patient with frontal lobe epilepsy (Laufs et al., 2006a).

Figure 3 shows an example of EEG-fMRI study in focal nonlesional epilepsy and validation with subsequent intracranial EEG recording.

The colocalization of the most significant BOLD changes within the resected volume has been related to a better outcome in small case series (Lazeyras et al., 2000; Thornton et al., 2009). Regarding the potential role of EEG-fMRI findings in clinical decision making, surgery or intracranial recording were reconsidered in 4 of 29 patients who had previously been rejected for poorly localized epileptic focus with use of other diagnostic modalities (Zijlmans et al., 2007).

In two patients with ictal EEG-fMRI recordings, intracranial EEG showed that ictal onset zone corresponded to the statistically strongest ictal BOLD change, providing complementary information to interictal studies (Tyvaert et al., 2008a).

Combination of ESI and EEG-fMRI

Intrinsic discrepancies between EEG and fMRI measurements

The combined analysis of electrophysiological and hemodynamic measurements always requires the awareness that the two datasets reflect observables differentially linked to the underlying neural activity, as discussed in Neurophysiologic Background. For example, as already mentioned above (Neurophysiologic Background), fMRI responses reflecting high metabolic activity can have no EEG correlate because of brain architecture such as deep-seated sources, source orientation tangential to the scalp, opposing source orientation in sulci. or concentric neuronal architecture (Connors & Gutnick, 1990). Furthermore, a nonsynchronized increase in neuronal activity would cause a metabolic increase but no change in the EEG trace. On the other hand, an EEG pattern without fMRI correlate is conceivable if a small proportion of a neuronal population behaves in a highly synchronized pattern without significant metabolic increase.

Furthermore, the BOLD signal arises due to oxygenation changes in both the microvascular tissue bed and the downstream venous pooling system, leading to potential responses in draining veins remote from the neural source. In anesthetized monkeys, sensory cortex mapping with fMRI and microelectrode arrays showed an overlap of 55%

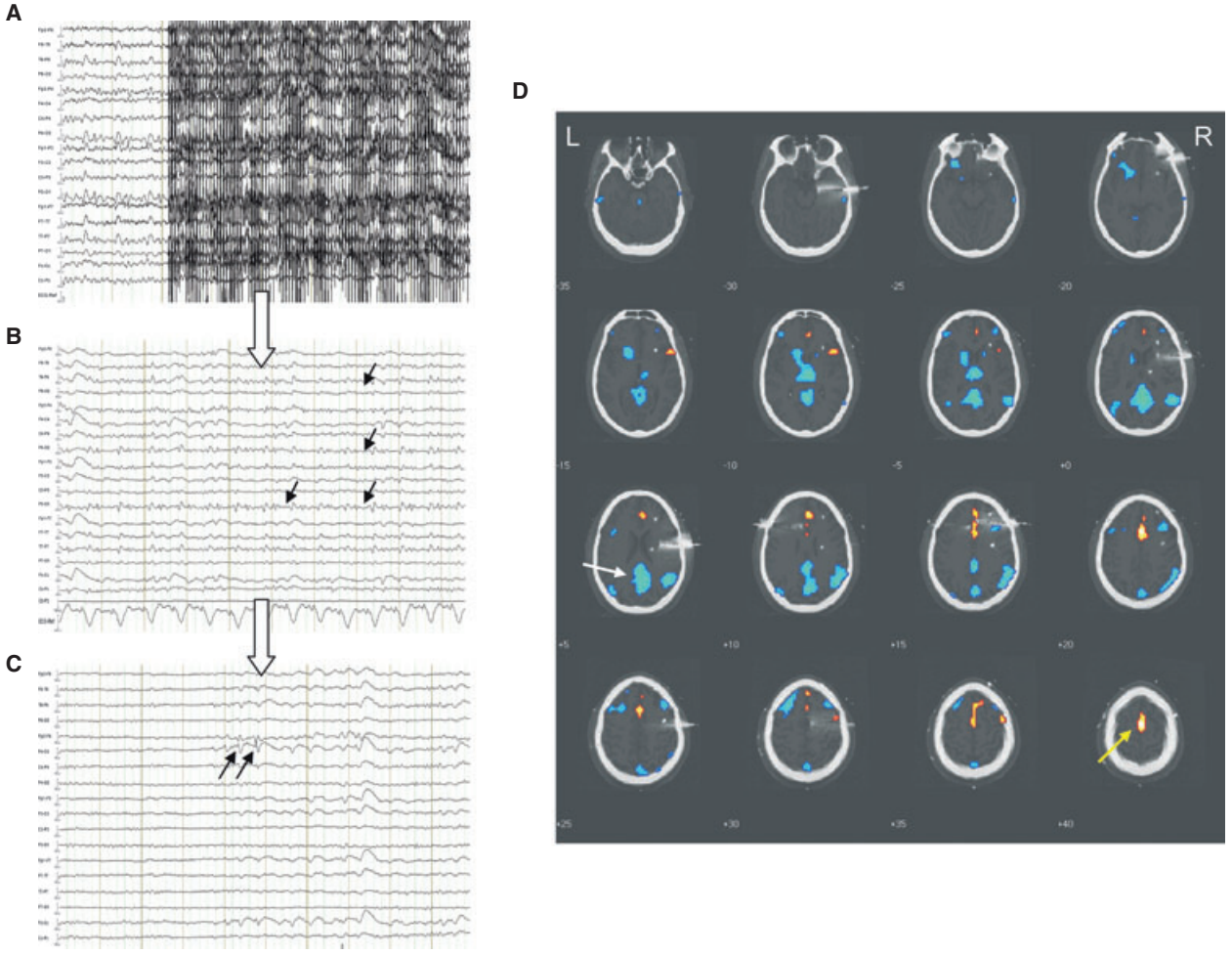

Figure 3.
Electroencephalography-correlated functional magnetic resonance imaging (EEG-fMRI) : 27-year-old man with nonlesional epilepsy and complex partial seizures starting with jerking of the left hand. (**A**) EEG recorded inside a 3T MR scanner with continuous slice acquisition shows prominent MR gradient–induced artifacts preventing analysis of the raw data. (**B**) EEG corrected for gradient-induced artifacts reveals the presence of significant cardioballistogram (arrows). (**C**) Subsequent EEG correction for cardioballistogram showing frequent right frontal interictal epileptiform discharges (IEDs, arrows). (**D**) Results of EEG-fMRI analysis show brain regions where the variance of the blood oxygen level dependent (BOLD) signal recorded with fMRI is statistically explained by the modeled BOLD response to IED. Images are coregistered to axial slices of T_1-weighted MRI of the individual patient with intracranial depth electrodes. There is a widespread network of BOLD changes (yellow-red clusters: positive BOLD changes, maximum in the supplementary motor cortex, yellow arrow; blue-white clusters: negative changes, maximum in the medial parietal cortex, white arrow) extending beyond the frontal lobe and in both hemispheres. Notably, there are negative BOLD changes in the thalamus and in the medial parietal cortex (precuneus), the latter corresponding to modulation in the default mode network time-locked to the IED.

(Disbrow et al., 2000), whereas in patients with epilepsy, intracranial EEG studies showed that IED sources and IED-correlated fMRI responses share spatial proximity but not exact concordance (Benar et al., 2006; Grova et al., 2008; Vulliemoz et al., 2009b) and the changes in neuronal activity related to distant BOLD responses are largely unknown, partly because these sites might not be sampled by intracranial electrodes. The coupling between neuronal activation, perfusion, and oxygenation seems to be preserved in the irritative zone (Stefanovic et al., 2005), including during IED (Carmichael et al., 2008a; Hamandi et al., 2008a), but this coupling is altered in electrographic seizures (Bahar et al., 2006). Structural brain lesions, notably of cerebrovascular origin, can affect neurovascular coupling (Rossini et al., 2004). This should be considered when modeling the BOLD response in regions potentially affected by abnormal hemodynamic properties (vascular lesions, vascular malformations, or tumors). Finally, there is puzzling evidence of regional cerebral blood flow changes prior to the onset of a stimulus and unrelated to intracranially recorded neuronal

activity (Sirotin & Das, 2009). Such changes have also been found prior to focal or generalized IED detected by scalp electrodes (Hawco et al., 2007; Moeller et al., 2008; Jacobs et al., 2009), suggesting early neurovascular changes preceding the IED undetected by scalp EEG.

In the following paragraphs, we discuss integrated inverse models of electromagnetic and vascular measurement. Such models have variously been developed to combine fMRI data with either EEG or magnetoencephalography (MEG) results. Although this review does not focus on MEG, we include relevant methodologic developments regarding a combination of MEG and fMRI. An advantage of EEG over MEG in multimodal fusion is the possibility of obtaining simultaneous recordings of EEG and fMRI, which is not possible with MEG. We also focus primarily on applications in patients with epilepsy, but refer to some developments in cognitive neurosciences that may be relevant to epilepsy imaging.

Symmetrical and asymmetrical combination of ESI and EEG-fMRI

There are various methodologic options for combining ESI or EEG and fMRI data, depending on the hierarchy that is applied to the analysis. First, in the classical EEG-fMRI analysis scheme (described in Data Acquisition and Processing) events of interest extracted from the EEG can be used as regressors for fMRI analysis and fusion of the two modalities is achieved through correlation in time in an EEG-informed EEG-fMRI modeling. In the spatial domain, the localizing capabilities of the two modalities offer the possibility of other forms of data fusion. As the general starting hypothesis is that a given aspect of scalp EEG and BOLD signals should be correlated over time in some parts of the brain, a degree of concordance between the two forms of localization is expected. Therefore, a sensible first step is to compare independently derived localizations via ESI and EEG-fMRI comparative studies, in which the EEG signal is used in parallel for both the analysis of the BOLD signal and the ESI to assess the degree of spatial concordance. Assuming a good degree of spatial concordance one may exploit the superior temporal resolution of EEG to try to reveal dynamic patterns in those regions. At a higher degree of integration, the results of one of the analyses can be used to constrain the other modality, resulting in an asymmetrical combination: Clusters of BOLD responses can be used to constrain ESI solutions obtained with underdetermined distributed source models: fMRI constrained EEG solutions. Conversely, ESI results can be used as predictors of the BOLD signal changes: ESI-informed EEG-fMRI analysis. Finally, based on the assumption that EEG and fMRI signals are generated by the same cortical region with a specific neuronoglial population, biophysical generative models can be developed to ''inverse'' both EEG and BOLD signals: Datasets of simultaneously acquired signals are entered into a comprehensive model of brain activity, neurovascular coupling, and resulting multimodal signals realizing a non-hierarchical symmetrical fusion model of EEG and fMRI (Daunizeau et al., 2009a).

ESI and EEG-fMRI comparative studies

Most studies comparing ESI and EEG-fMRI localization are based on recordings obtained from separate sessions: EEG-fMRI is often recorded with a relatively small number of scalp EEG electrodes, and ESI is performed on data obtained with better electrode coverage outside the scanner environment. The first validation of EEG-fMRI findings in epilepsy was reported by Seeck and others using ESI (distributed inverse solution) and intracranial recording in one patient (Seeck et al., 1998). Lemieux et al. (2001) compared the localization of IED-related BOLD responses and EEG source localization in six patients (five with lesions). They used spike-triggered fMRI and compared the results with ESI based on 64-channel EEG acquired separately outside the scanner. Two different models of equivalent dipole sources were used with a realistic head model. The concordance between both modalities was generally good. In all cases, at least one dipole was located in the same lobe for each BOLD cluster, with an average peak distance of 2.2 cm for positive and 3.5 cm for negative responses. Concordance of EEG-fMRI results with lesion localization was also good, but no intracranial recording was available for validation.

In a similar study, Bagshaw et al., (2006) performed spatiotemporal dipole modeling and EEG-fMRI in 17 patients. Distance between the equivalent dipole and the closest activated voxel was 32–34 mm, but was much greater when the most active voxels were considered (58.5–60.8 mm). The authors pointed correctly to the mislocalization resulting from the dipolar model assumption, which tends to result in sources out of the gray matter and deep into the brain. In another study from the same group, Benar et al. (2006) studied the concordance between EEG-fMRI BOLD clusters, ESI, and intracranial EEG (stereotactic depth electrodes or subdural grid electrodes) in five patients, some of them included in the previous study. In both studies, EEG for ESI was recorded in a separate session, after adding 21 electrodes to the 19 electrodes used inside the MR scanner and ESI was based on multiple dipolar sources and a realistic head model. The main finding was that whenever there was an intracranial electrode in the vicinity (20–40 mm) of positive or negative BOLD clusters or ESI, this electrode recorded epileptic activity. There was better concordance between BOLD clusters and intracranial EEG than between ESI and intracranial EEG, stressing the limitation of equivalent current dipole (ECD)-based ESI models, as well as the sampling limitations of intracranial EEG. In the temporal lobe, however, some ESI sources had no BOLD correlate, and the reverse was also found, with isolated BOLD clusters in the supplementary motor cortex. In both studies, no information was given regarding the most active BOLD cluster, the main ESI source, and the main intracranial focus.

Although no clear-cut match between intracranial EEG and BOLD changes is expected (Disbrow et al., 2000), these distances are clearly larger than those from studies comparing the localizations of BOLD response and ECD source models of evoked responses to external stimuli.

With the preceding considerations in mind, distributed source models might be better suited for widespread IED, more likely to be associated with significant BOLD responses. A more refined study on the same patient group as that of Bagshaw et al. used geodesic distance to measure concordance between BOLD cluster, a distributed source localization, and a Bayesian framework to assess fMRI concordance and relevance. It showed a good concordance between ESI and BOLD for 24% of BOLD cluster in six of seven patients, with intracranial EEG validation in three patients (Grova et al., 2008).

In a series of 11 children with benign rolandic epilepsy, Boor et al., (2007) compared the results of spatiotemporal dipole modeling with EEG-fMRI BOLD patterns (using a parametric estimate of the spike frequency, and interleaved MR acquisition with no artefact correction), again from two separate acquisition sessions. In 4 of 11 patients, BOLD clusters were concordant with the locations of the initial dipoles, and additional areas of activation extended into the central fissure and the insula in three of these patients, concordant with dipolar sources of propagated activity. The authors concluded that ESI helped to define a pattern of propagation of IED in the EEG-fMRI results.

An important methodologic issue in all these studies is the choice of a threshold for the different techniques, which becomes particularly crucial when assessing concordance (overlap) between modalities.

Comparing results of ESI and EEG-fMRI performed on separate recordings raises some methodologic issues. Even when the antiepileptic drugs are unchanged between recording sessions, the frequency, spatial distribution, and morphology of IEDs can be critically modified by attention and arousal level, time since the last seizure, and other changes of the background cerebral activity. Analysis of the same EEG recording by both methods is essential if effects of individual IED are to be studied. However, ESI on IED recorded during fMRI acquisition could be affected by MRI-induced artifacts and any method employed to reduce the artifact (Grouiller et al., 2007). Two recent studies with similar methodology used EEG recorded during fMRI acquisition in groups of adult (Vulliemoz et al., 2009b) or pediatric patients (Groening et al., 2009) with epilepsy. In both studies, ESI applied to the EEG recording during the fMRI acquisition after correction for MR-gradient and pulse-related artifacts showed robust results, concordant with other available noninvasive information (semiology, video-EEG telemetry, structural MRI, and in the pediatric group: also PET/SPECT). ESI results identified distinct BOLD clusters associated with IED onset and propagation of IED, providing information regarding the temporal dynamics between BOLD clusters and illuminating the complex pattern of BOLD signal changes related to IED. The additional BOLD clusters spatially unrelated to ESI probably reflect a distant modulation of neuronal activity and metabolism time-locked to IED rather than propagation of epileptic activity per se. Intracranial EEG recordings in three of eight of the adult patients were concordant with these findings.

Figure 4 shows how a combination of ESI and EEG-fMRI can be used to gain temporal information about the multiple clusters of BOLD changes related to IED with validation from intracranial EEG recordings.

"*fMRI-constrained ESI*"

The ill-defined nature of the EEG inverse problem undermining ESI can be addressed by making a priori assumptions on the nature of the generator. Constraining ESI solutions based on knowledge derived from fMRI results have been considered particularly in cognitive neuroscience (Ahlfors et al., 1999; Babiloni et al., 2002; Liu et al., 2006). Similar developments have taken place in the field of the MEG inverse solution (Ahlfors et al., 1999; Dale et al., 2000). However, in general, the application of fMRI constraints to ESI should be considered with caution due to the absence of validated biophysical fusion models. Starting with an EEG-based inverse solution and applying fMRI-based constraints to the solution in order to increase agreement with fMRI data carries the risk of spatial bias with false-positive and false-negative solutions (Brookings et al., 2009). Moreover, the "static" fMRI constraint will be applied to successive EEG time frames with different scalp maps and source activity (Gonzalez-Andino et al., 2001). Preliminary studies with dipolar constrained ESI have shown good correlation with focal fMRI results. However, fMRI-constrained ESI in the case of spatially distributed networks remains a difficult challenge. Some recent studies suggest that distributed ESI is more suited than dipolar ESI when large areas of cortex are involved (Grova et al., 2008, Liu & He, 2006). Currently, when studying epileptic activity, an fMRI-informed constraint on ESI is not recommended, unless it includes flexible weighting and proper model comparison tools to assess the relevance of the BOLD clusters as ESI priors, for instance within a Bayesian framework for an a posteriori assessment of the relevance of the fMRI constraints (Daunizeau, Grova et al., 2006).

A recent study compared the localization of the separate generators of the spike and wave components in generalized spike wave discharges (GSW) using simultaneously acquired EEG-fMRI. GSW-related BOLD clusters were used as priors in a Bayesian EEG source model comparison (Daunizeau et al., 2009b). Spikes and slow waves components of GSW were associated with different clusters of BOLD response, suggesting that distinct neuronal networks generate these excitatory (IED) and inhibitory (slow wave) processes or are affected by them.

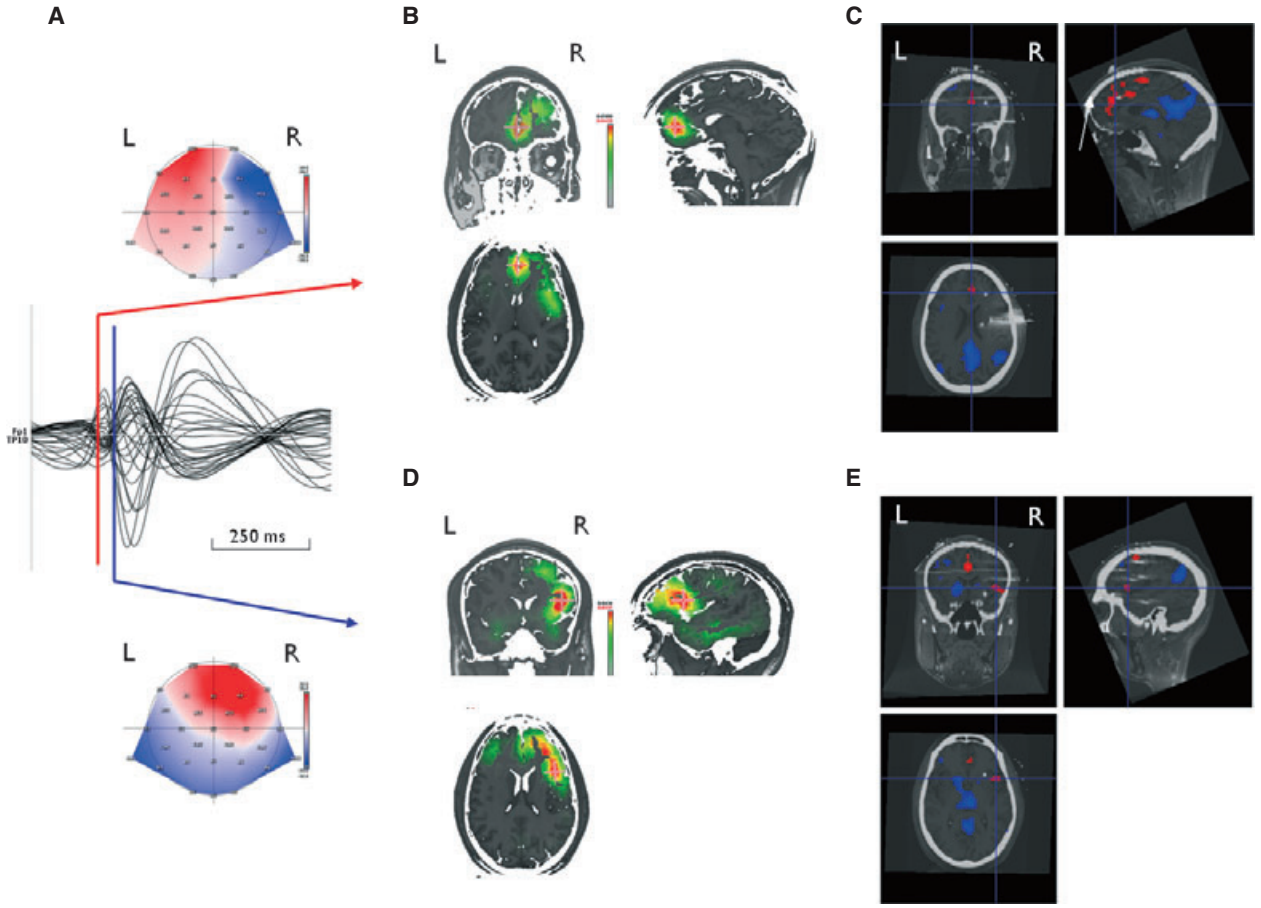

Figure 4.
Combination of electroencephalography (EEG) source imaging (ESI) and EEG-correlated functional magnetic resonance imaging (fMRI). ESI allows the addition of temporal information to EEG-fMRI results and discrimination between blood oxygen level dependent (BOLD) clusters associated with early versus late components of interictal epileptiform discharges (IEDs). Same patient as in Fig. 3. (**A**) Averaged IED recorded inside MR scanner during fMRI acquisition. The first rising phase of the averaged IED is used to localize IED onset (ESIo, red line, top map of EEG scalp voltage topography) and a later timeframe for IED propagation (ESIp, +88 ms, second rising phase of the averaged IED, blue line, bottom map of EEG scalp voltage topography). (**B**) ESI at IED onset is localized in bilateral medial frontal cortices. (**C**) EEG-fMRI results (red/blue, positive/negative BOLD changes): there is a right medial frontal positive BOLD cluster concordant to ESI at IED onset (cross-line at cluster maximum); intracranial depth electrode confirmed this region as the maximum of the irritative zone. (**D**) ESI of later timeframes shows a shift of maximal source activity to right frontal-opercular region; (**E**) right lateral frontal positive BOLD cluster closest to ESI of IED propagation (cross-line at cluster maximum)

"*ESI informed fMRI analysis*"

Using the reverse analytical asymmetry, ESI results can be used for fMRI analysis in the general linear model. Liston et al. (2006) combined EEG source imaging and fMRI with the objective of improving sensitivity and reducing EEG observer bias in one patient. They used an automated spike classification and subsequently projected the EEG in the source space on an equivalent current dipole with an amplitude threshold (ECD). An additional 61% of IEDs were detected, thus increasing the explained variance of the MR signal. In a similar study, continuous ESI of the region of IED onset explained a significant amount of additional BOLD signal variance in 10 of 15 cases, concordant with other noninvasive modalities or intracranial EEG (Vulliemoz et al., 2009a). Continuous ESI appears, therefore, to refine the model of the neuronal activity of the irritative zone and its hemodynamic correlates. This could have important implications for the clinical role of EEG-fMRI in candidates for epilepsy surgery.

Neural mass models and "symmetrical fusion model of EEG and fMRI"

In principle, EEG and fMRI data could be used to estimate fusion models relating BOLD signal and scalp EEG

signals to underlying neuronal activity (Trujillo-Barreto et al., 2001; Daunizeau et al., 2007; Brookings et al., 2009). The inversion of these two forward models could lead to a symmetrical fusion of EEG (or MEG) and fMRI data that could better localize active neural sources. This requires a detailed model of the relationship between neuronal activity and hemodynamic response, which is generally based on neural mass models and a variant of the ''balloon model'' (Buxton et al., 1998; Babajani & Soltanian-Zadeh, 2006). Recent work in this field relies mainly on simulated data to generate event-related potentials in response to a stimulus with no current application to epilepsy (Deneux & Faugeras, 2006; Sotero & Trujillo-Barreto, 2007; Valdes-Sosa et al., 2009).

Figure 5 shows the principle of such fusion models and the underlying neural mass model. Applied to patients with epilepsy, these models could help understanding of the dynamics of neuronal and metabolic activity throughout the brain regarding initiation, propagation, and termination of epileptic activity. They could also potentially be valuable tools to study the effect of antiepileptic drugs on these neuronal networks.

Methodologic perspectives

EEG-fMRI and ESI studies in the frequency domain

The BOLD signal correlates of physiologic scalp EEG rhythms have revealed distinct patterns of ''resting state activity,'' both in healthy subjects (Mantini et al., 2007) and in patients with epilepsy (Tyvaert et al., 2008b). Theoretical work suggests that an increase of neuronal activity is associated with a shift of the frequency spectrum toward the high frequencies and regional BOLD signal increases (Kilner et al., 2005). Frequency-based approaches have been applied to ESI of ictal EEG (Lantz et al., 1999; Blanke et al., 2000) as well as to EEG-fMRI recordings (Salek-Haddadi et al., 2003; Laufs et al., 2006a; Siniatchkin et al., 2007) with promising results, but combined ESI and EEG-fMRI approach in the frequency domain are still lacking.

Cortical potential imaging

Scalp EEG data can be also used to reconstruct cortical potentials using realistic head models, and it has been suggested that the use of fMRI-weighting of the cortical potential computation could help to increase the spatial resolution

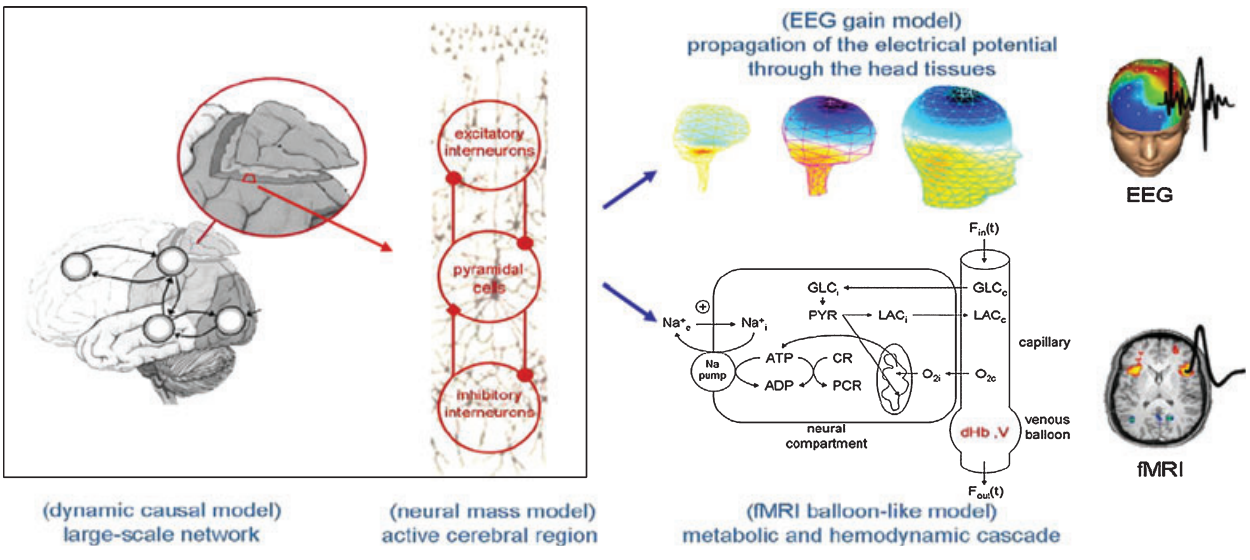

Figure 5.
Principle of symmetrical fusion model of electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) (neurophysiologically and biophysically grounded generative model of both EEG and fMRI data) involving many levels of description. At the mesoscale of local neuronal population (pyramidal cells and interneurons), neural mass models describe the dynamics of local excitatory and inhibitory connections (intrinsic connectivity) (Kiebel et al., 2007). The interactions between neuronal populations and brain regions (macroscale, extrinsic connectivity) forms the basis for dynamic causal modeling (DCM) (Friston et al., 2003). The EEG signal is predicted by computing the instantaneous electrical potential generated by the pyramidal cells, which has spread through the head volume (volume conduction). At the microscale (cellular) level, the fMRI signal is the end result of a metabolic and hemodynamic cascade occurring over a time scale of seconds (Riera et al., 2006). Symmetric fusion models rely on finding inverse solutions of these models to estimate the neuronal activity and connectivity of the underlying neuronal population. Reprinted from: NeuroImage 40(2), Laufs, H., Daunizeau, J., Carmichael, D. W. and Kleinschmidt, A., Recent advances in recording electrophysiological data simultaneously with magnetic resonance imaging, pp 515–28 Copyright 2008, with permission from Elsevier.

(Liu & He, 2006). This technique has been used to map evoked potentials with validation through intraoperative electrocorticography (He et al., 2002). Its application to interictal discharges could provide valuable information in the context of cortical mapping in epilepsy surgery candidates.

Can fMRI time resolution inform about network dynamics without electrophysiologic recording?

The sampling frequency of the fMRI signal and the slow response of the HRF limit our ability to study fast changes in neuronal activity, which occur at the time scale of milliseconds. Focal perfusion and metabolic changes have been observed before the occurrence of detectable scalp EEG events and suggest a facilitating role of slower processes in the generation of focal and generalized epileptic activity (Hawco et al., 2007; Moeller et al., 2008; Jacobs et al., 2009). Dynamic causal modeling (DCM) (Friston et al., 2003) is an analytic tool recently developed to study directionality and causality relationships between fMRI activation clusters (Fig. 5). Initially developed to model the response of neural populations to an external stimulus, such as in cognitive fMRI, DCM has recently been validated in animal models of epileptic activity (David et al., 2008) and applied to human epileptic brains to identify neural drivers of intracranial EEG or fMRI signals (Hamandi et al., 2008b; Vaudano et al., 2009). Identifying the directionality of the interaction between brain structures revealed with fMRI, thanks to a comprehensive underlying neuronal model, would be a major step in understanding the dynamics of epileptic networks. This could help bridge the gap between our understanding of epileptic activity at a cellular level and on a whole-brain scale.

Conclusions

As a direct imaging tool of neuroelectric activity, the localizing value of ESI in the presurgical work-up of patients with epilepsy has been validated by several intracranial EEG studies and surgical series. Recent studies also suggest a good concordance between EEG-fMRI findings and similar gold standard localization tools. Studies comparing or combining ESI and EEG-fMRI suggest that the combination of these techniques can provide new localizing and temporal information, with potential clinical relevance. There are exciting ongoing biophysical modeling and experimental developments attempting to solve the combined ''electrovascular inverse problem'' and to uncover the precise nature of microscopic and macroscopic neurovascular coupling. Their future translation from group studies of cognitive evoked-related potentials to individual patients with spontaneously occurring epileptic discharges is far from simple but will likely help us to better understand the underlying mechanisms of the generation, propagation, and termination of epileptic discharges. The assessment of clinical relevance, especially with respect to epilepsy surgery planning, will be required through intracranial studies or postoperative follow-up. These techniques may also have wider application in the investigation of the interaction between epileptic activity and other brain networks involved in resting state, cognitive processes, and sleep.

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